Properties of brain tubulin in the perspective of quantum information processing

Synopsis
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Introduction

The classical theories of information processing in the brain, fail to explain its speed and complexity. Hence, the idea of the brain working as a quantum computer was put forth by the mathematician Roger Penrose in the late 20th century. Prof. Nancy Woolf endorsed this idea and further observed that neuropsychiatric disorders cannot be fully explained by the theories that we have today (N J Woolf, Craddock, Friesen, & Tuszynski, 2010). Stuart Hameroff, along with Penrose, proposed a theory that quantum information processing takes place in microtubules. Microtubules are hollow cylindrical polymers of the tubulin heterodimer. They are a part of the cytoskeleton and are ubiquitously found in all organisms, from protists to human beings. There are about 10^9 tubulin molecules per neuron. Neuronal microtubules are good candidates for memory storage (Hameroff and Penrose, 2014).

The αβ tubulin heterodimers polymerise longitudinally to form a protofilament. These protofilaments are arranged helically to form microtubules (Li, DeRosier, Nicholson, Nogales, & Downing, 2002). The amino acid sequence of α and β tubulin is highly conserved in all eukaryotes. However, tubulin diversity is achieved in two different ways: (1) expression of different α and β genes, called tubulin c; and (2) generation of post-translational modifications, called tubulin isoforms. This heterogeneity affects microtubule function. (Janke, 2014). Microtubules have been shown to play a key role in diverse functions, like in cell growth, cell division, cell shape, cell motility, intracellular transport, organelle positioning, in cilia and flagella, ciliopathies, cancer and learning and memory, to name a few (Woolf, 2006).

The use of recent technology has made it possible for us today, to actually visualise dynamic instability in microtubules and show that microtubules might be important for neuroplasticity, which is the ability of brain cells to modify themselves, as a response to intrinsic and extrinsic factors (Shaffer, 2016). Studies using 2-photon microscopy have shown that they penetrate into the dendritic spines (Dent, Merriam and Hu, 2011). This has been observed in both cortical and hippocampal neurons. Recent studies by Hameroff et al has unfolded the function of microtubules in a whole new light where information processing is concerned (Hameroff and Penrose, 2014).

Bandyopadhyay's group has experimentally confirmed the possibility of quantum phenomena in microtubules (Sahu, Ghosh, Fujita, & Bandyopadhyay, 2011 and Sahu, Ghosh, Fujita, & Bandyopadhyay, 2014). In a book called Emerging Physics of Consciousness, in 2006, Behrman et al (Behrman, Gaddam, Steck and Skinner, 2006) published computational model of a quantum hopfield network model of microtubules, based on the Penrose-Hameroff Orch OR theory. Hopfield neural networks consist of networks of non-linear graded response neurons with symmetric synaptic connections. In this simulated model, they had represented qubits as tubulin heterodimers with mutual coulombic interactions with each other. Qubits are the fundamental unit of information in a quantum computer. Like bits are binary, qubits are quaternary in nature, i.e. bits exist as 0 or 1 and qubits exist as 0 or 1 (like a classical bit) and in the states corresponding to the superposition of 0 and 1. In other words, qubit exists as both 0 and 1, with a numerical coefficient that represents the probability for each state). This is because the qubit follows the principles of quantum mechanics and not classical physics (Srivastava, Sahni and Satsangi, 2009). In the same book, Prof. Nancy Woolf had suggested five levels of quantum entanglement in the brain, i.e.: quantum entanglement (1) between tubulin molecules within a microtubule, (2) between two microtubules in a single neuron, (3) between neurons in a module, (4) in highly interconnected cortical areas and (5) among cortical areas with negligible axonal connections.

Recently, higher dimension quantum processing unit "a qudit" have shown higher tolerance for noise and have the ability to store more information than qubits (Groblacher, Jennewein, Vziri, Weihs and Zeilinger, 2006). Qudits are defined as density matrices of d–dimensional quantum systems (Bertlmann and Krammer, 2008). Matrices are a mathematical representation of vectors in multiple dimensions (Solo, 2010). A density matrix is a type of matrix used to describe quantum systems in a mixed state, which is a group of several quantum states (Fano, 1957).

Based on the works of Behrman et al and Woolf et al (mentioned above), Srivastava et al created a mathematical model of brain microtubules as an n-qudit quantum hopfield network; and illustrated how this model could be used for higher abstraction in mathematical modelling of consciousness (Srivastava et al, 2016).

Experimental evidence of quantum behaviour of microtubules comes from AFM studies of tubulin by Bandyopadhyay's group (Sahu et al, 2014). However, the dynamic state of the tubulin molecule and the coherent energy transfer between its superposition (electronic) states (*i.e.* excitonic states) still remains to be understood, analogous to pigment (chlorophyll) molecules encountered in photosynthetic energy transfer (Dawlaty et al, 2012). Hameroff and Craddock et al (Hameroff and Penrose, 2014; Craddock et al, 2014) have however, computationally illustrated the role of tubulin (with a special emphasis on tryptophan) in quantum information processing. The other amino acids have not been studied. Bandyopadhyay's group has shown that the presence of a water channel in microtubules is imperative for quantum phenomena to be observed. Among other molecules, it has been shown that tryptophan is involved in electron transfer and water channel plays a key role in proton transfer (Chen et al, 2013; Winkler et al, 2014). The two studies seem to somewhere contradict each other.

Microtubules have also been mathematically modelled as n-qudits (Satsangi et al, 2016). However, the physical realisation of the qudit is lacking so far. We conjecture that delocalization similar to that in the photosynthetic systems, may lead to the coherent electron/proton transfer mediated via the tubulin heterodimer. In order to study quantum information processing in the brain, in the present proposal we propose to (1) perform *in vitro* studies by doing spectroscopic analysis to study quantum behaviour of tubulin (2) do simulations for i*n silico* analysis of quantum behaviour of tubulin and (3) explore information processing in brain through the notion of a qudit (which is n superposed states of tubulin heterodimer (Srivastava, Sahni and Satsangi, 2016)) and mathematical abstraction.

Review of Literature

The review of literature is divided in sections as the study is multidisciplinary in nature. The sections include (1) tubulin and microtubules (2) quantum and quasi-classical biology (3) quantum information processing (qubits and qudits) and (4) quantum information processing in microtubules.

Tubulin and Microtubules

Lowe, Downing and Nogales (2001) analysed the structure of tubulin at 3.5A resolution. α and β tubulin dimerise to form the tubulin heterodimer. The two share 40% of their amino acid sequence. Both of them have 3 domains: one near the N- terminal, one near the C-terminal and an intermediate region. The one near the N-terminal has the nucleotide-binding region. The domain near the carboxy-terminal has the microtubule associated protein (MAP) binding region. The intermediate domain binds to the drugs colchicine and taxol. The tubulin heterodimer has 2 β-sheets in the core that are surrounded by 12 α- helices.

Janke (2014) deciphered the tubulin code. He reported the myriad forms of tubulin exists due to two reasons; first is the expression of different α and β genes (which gives the different tubulin isotypes); second is by differential post-translational modifications (PTMs) of the tubulin C-termini. There are 8 α-tubulin genes and 12 β-tubulin genes in humans.

Verdier-Pinard et al (2012) demonstrated many types of tubulin (the different isotypes and isoforms) However, only a certain number of them are actually expressed in the cell. Matrix assisted laser desorption ionisation- Time of flight (MALDI-TOF) analysis has shown that β-III tubulin is specifically found in the brain. Low concentrations of β-II tubulin have been detected in the brain, though it is primarily found in other neurons. **Ait-Belkacem et al** (2013) used MALDI in-source decay to identify the various tubulin isoforms present in the brain. They found tubulin α1a, α1b, α1c,β_{IV} and β_{V}

Alushin et al. (2014) reported high resolution cryo-electron micrographs of microtubules (4.7-5.6Å). They have described that the tubulin heterodimers form a protofilament, (typically) 13 of which make a hollow cylindrical structure, the microtubule. They also found microtubules with 9-16 protofilaments. The protofilaments in microtubules are arranged in a helical fashion.

According to **Kapitein and Hoogenraad** (2015), neurons are rich in microtubules. They are found as arrays in axons and dendrites. They provide a structural backbone for axons and dendrites that allows them to acquire and maintain their specialized morphologies. They have discussed the importance of microtubules in developing and adult neurons and their role in alterations in dendritic morphology that may correspond with neuroplasticity even in old age.

Dent, Merriam and Hu (2011) have thrown light upon the key role played by microtubules in neuroplasticity. On the surface of dendrites, there are small protrusions called dendritic spines whose plasticity is important for learning and memory. Earlier work had mostly given importance only to the role of actin filaments. However, with the advent of modern technology, recent data suggests the importance of microtubules.

Quantum and Quasi-Classical Biology

Arndt, Juffmann and Vedral (2009) and **Lambert et al** (2012) have reviewed the concept advent and advantages/applications of quantum biology. The idea that quantum mechanics might play a role in biology may appear radical at first. However, it cannot be denied that all chemical processes depend on quantum mechanics. Quantum physics and electro-dynamics determine the shape of molecules and thus, have an impact on molecular recognition and functioning of molecules like DNA and proteins. It has been shown that quantum phenomena could exist in living systems under certain conditions. For example, (1)They can occur in hydrophobic pockets of proteins (2) Quantum error correction can take place if there are many qubits (3) Quantum phenomena can exist if there is local cooling, which they say is possible as living systems are open systems and/or (4) If entanglement if refreshed faster than decoherence can take place, entanglement will persist. Quantum phenomena have been observed in many molecules in biological systems, eg in Deoxyribonucleic Acid (DNA), migration of birds and photosynthesis.

Marcus et al (1985) have given a relationship between the rate of electron transfer and the molecule's Gibbs' free energy. Winkler and Grey (2015) have thrown light on the importance of Try and Trp in electron transfer. Chen et al (2000) have described proton transfer in proteins. They have described

proton wires (made of water molecules and protonatable amino acid side-chains.) in bacteriorhodopsin and and cytochrome c.

Quantum Information processing

According to **Sahni, Srivastava and Satsangi** (2009), the theory of classical information, computation, and communication developed extensively during the twentieth century, cannot fully characterize how information can be used and processed in the physical world—a quantum world. They describe that in the case of quantum information processing, the fundamental unit of information is called a "qubit" (quantum bit). While a classical bit can only assume the values of 0 or 1, a quantum bit can have any value that lies between 0 and 1. This is because of quantum superposition. This is written as $|\psi> = \alpha| > \text{ and } \beta< |$. Where, α and β are probability amplitudes. They have mathematically represented the qubit. They used graph theory, a branch of topology, to give a unified model of representing qubits. They used graph theory to represent field problem as a circuit problem by discretization.

Bertlmann and Krammer (2008) defined qudits as density matrices of d–dimensional quantum systems. They have described three types of matrix bases that can be used to decompose qudits, i.e., the generalized Gell- Mann matrix basis, the polarization operator basis, and the Weyl operator basis. According to them, such a decomposition can be identified with a Bloch vector which is a a generalization of the qubit case. The d-dimensional quantum states, or qudits, could be more efficient in quantum applications because (1) they may improve the capacity of channels (Luo et al, 2014) (2) implementation of quantum gates (Luo et al, 2014)(3) increase security (Groblacher et al, 2006) (4) They can tolerate more noise and (5) have the ability to store more information than qubits (Groblacher et al, 2006) **Howard, Wallmann, Veitch and Emerson** (2014) have discussed the significance of contextually in quantum computation. Contextuality is an intrinsic attribute of the quantum theory and plays an important role in characterizing the aptness of quantum states for magic state distillation.

Quantum Information Processing in microtubules

Hameroff and Penrose (2014) proposed the idea of quantum computation in the brain and suggested that classical computing could not possibly explain the powers of the human brain. They put forth the Orchestrated Objective Reduction theory (OrchOR). Quantum phenomena are used to solve complex computational problems. They further emphasize that memory should be stored in microtubules as they are (1) ubiquitously found in all organisms, including protists (2) microtubules are highly concentrated in neurons (3) there are 10^9 tubulin molecules per person (4) neuronal microtubules are capped by MAPs which makes them rather stable. Hence, according to Hameroff et al, they are good candidates for memory storage.

Tuszynski's group has worked in close association with Hameroff and have used computational biology to understand the role of microtubules in information processing and consciousness. They proposed a model of encoding of memory in microtubules with calmodulin dependent protein kinase II (CAMKII) phosphorylation (Craddock, Tuszynski and Hameroff, 2012). He showed the importance of Tryptophan in quantum phenomena in tubulin and microtubules, in 2014 (Craddock, Priel and Tuszynski, 2014) and in 2015, he modelled how anaesthetics act on quantum channels in microtubules (Craddock, Hameroff, Ayoub, Klobukowski and Tuszynski, 2015).

Nancy Woolf et al (2010) have discussed how neuropsychiatric disorders cannot be fully explained by the many theories that we have today. According to Woolf et al, these diseases can only be completely understood with the help of quantum information processing theories.

Experiments by **Anirban Bandyopadhyay's group** (2011) elegantly demonstrated that Frohlich condensation can take place in microtubules. The change in the length of a coherent system should not have any impact on its resistance. . Bandyopadhyay demonstrated such a phenomenon for microtubules in vitro, in addition to this, conductivity remain unaltered either with change in temperature. The authors , therefore predicted massively-parallel, non-central distributive computing in the brain. However, they were unable to explain how this originated, however concluding that microtubules could be a possible candidate. In 2013 (Sahu et al., 2013), the same group studied

tubulin and microtubule, with and without water. Interestingly, they found evidence that quantum coherence is found in microtubules.

In 2014 (Sahu, Ghosh, Fujita, & Bandyopadhyay, 2014), the same group claimed to have observed quantum tunnelling in microtubules. They did not add any GTP or Mg^{+}. The authors found that neighbouring tubulin heterodimers self-assembled to form a protofilament from solution of pure tubulin, which then formed a 2D sheet. They used 64 combinations of different tubulin molecules derived from plants, animals and fungi; and many doping molecules. They repeatedly observed the common frequency region (that was reported earlier) where the protein folded mechanically and vibrated electromagnetically.

Srivastava, Sahni and Satsangi (2016) extended the model proposed by Behrman et al and have modelled brain microtubules as an n-qudit quantum hopfield network. They have derived equations that represent the qubit as a loop and the qudit as a sphere. According to them, there should be different types of qudits that make up the n-qudit. However, the molecular understanding of the differences in qudits remains to be elucidated. The experimental demonstration microtubules as n-qudits has not been reported. This motivated us to pursue the problem with an objective to demonstrate the existence of qudit with wider biological perspective.

Objectives

In order to understand the direct role of microtubules and their constituent tubulin heterodimers, in information processing, the concept of 'qudits', *i.e.* d-dimensional quantum superposition states of tubulin heterodimers, has been envisaged mathematically (Srivastava, Sahni and Satsangi, 2016). This would explain the speed and complexity of information processing in the brain, that still remains unexplained by our classical theories. Their is a possible existence of a 'quantum' mechanism, analogous to the coherent energy transfer between superposition (electronic) states (*i.e.* excitonic states) of pigment (chlorophyll) molecules encountered in photosynthetic energy transfer (Dawlaty et al, 2012). Based on the studies of Srivastava et al (2016), Hameroff et al (2014) and our preliminary work on the inherent potential of the tubulin heterodimer for coherence and tunnelling, we conjecture that delocalization, similar to that in chlorophyll, may lead to the coherent electron/proton transfer mediated via the microtubule cytoskeleton. In order to study quantum information processing in the brain, the specific objectives are as follows:

1. Expression
    i. Expression and purification of tubulin
    ii. Characterisation of expressed tubulin
    iii. Analysis of the purified tubulin through spectroscopy to understand the quantum properties of tubulin
2. Simulation: In silico analysis of tubulin and microtubules through molecular dynamics to study the phenomenon of quantum tunnelling.
3. To explore information processing in brain theoretically, through the notion of a qudit and mathematical abstraction

Flow of Work

Objective 1

1. Expression and characterisation of tubulin
    a) Modified pUC19 plasmid will be obtained
    b) Recombinant human tubulin dimer will be expressed using baculovirus system
    c) SDS-PAGE, western blot and mass spectrometry analysis/N-terminal sequencing
2. Spectroscopic analysis of purified tubulin for quantum behaviour by spectroscopy/spectroscopies like circular dichroism/scanning tunnelling/Raman/Time-resolved Raman

Objective 2

1. The PDB file of tubulin will be obtained from Protein Data Bank
2. In silico mutants
    a) Generation
    b) Visualisation and analysis
3. Post-translational modifications (PTMs)
    a) Creation of PDB files of tubulin with different PTMs
    b) Simulation of the generated PDB files
    c) Visualisation and analysis of the simulated protein
4. Analysis of significance of number of tubulins in quantum information processing
    a) Creation of PDB files of polymers/chains of n number of tubulin to study the significance of odd prime number of tubulins with original tubulin PDB file, obtained from Protein Data Bank
    b) Simulation of generated PDB files
    c) Visualisation and analysis of the files obtained after simulation

Objective 3

Theoretical study through mathematical abstraction

Methods

The methods are discussed below, corresponding to the objectives:

Corresponding to objective 1:

Step 1: Human tubulin will be expressed, purified and characterised on the basis of the protocol by Minoura et al, 2013.

1. The plasmid with tubulin gene that will be used are pmKate2-Tubulin (GFP) and pPaxillin-mKate2 (RFP) (gift from Dr. Yawer, St Louis).
2. Recombinant human tubulin dimer will be prepared using modified pUC19 plasmid in. Bac-to-Bac system.
3. Characterisation of expressed protein will be done by SDS-PAGE & Western blot & Mass spectrometry analysis/ N-terminal sequencing

Step 2: Spectroscopic analysis would be done to understand the quantum phenomena in tubulin, using spectroscopy/spectroscopies like:

Technique	Advantage	Reference
Circular dichroism	For studying the secondary structure of tubulin	Micsonai et al, 2015
Scanning tunnelling spectroscopy	For understanding charge and spin transport	Ervasti et al, 2017
Raman spectroscopy	To understand the chemical composition and molecular structure of tubulin	Butler et al, 2016
Time-resolved Raman spectroscopy	To study the various conformational states of tubulin	Lecomte et al, 1998

This objective will be done in collaboration with IISER Mohali

Corresponding to objective 2:

Step 3: Obtaining the PDB file of tubulin from Protein Data Bank. The text file will be downloaded.

Step 4: Generation of *in silico* mutants with the help of Rotamer function of UCSF Chimera (Huang, Meng, Morris, Patterson and Ferrin, 2014).

Step 5: They will be simulated with the help of a molecular dynamics packages like GROMACS (Abraham et al, 2015). Their potential energies, coulombic interactions, lennard-jones interactions etc.will be analysed. The PDB and the .gro files will be visualised with the help of software like PyMOL (Schrodinger, 2016) and or UCSF Chimera (Huang, Meng, Morris, Patterson and Ferrin, 2014).

Step 6: The PDB files and the resultant files of the simulations will be visualised with the help of visualisation software like PyMOL (Schrodinger, 2016) and or UCSF Chimera (Huang, Meng, Morris, Patterson and Ferrin, 2014).

Step 7: Creation of PDB files of tubulin with:

1. different post-translational modifications
2. post-translational modifications of different lengths

This will be done with the help of software like PyTMs (Warnecke, Sandalova, Achour and Harris, 2014).

Step 8: The PDB files thus created in step7 will be simulated and analysed with the help of a molecular dynamics package GROMACS. The resultant files will be visualised with PyMOL and/or UCSF Chimera. This will be similar to step 5.

Step 9: Creation of PDB files of polymers/chains of n number of tubulin to study the significance of odd prime number of tubulins with

1. original tubulin PDB file, obtained from Protein Data Bank
2. PDB files created in step 7

Step 10: The files created in step 9 will also be simulated with the help of a molecular dynamics package like GROMACS. The resultant files will be visualised with PyMOL and/or UCSF Chimera. This, too, will be similar to step 5.

Corresponding to objective 3:

Step 6: Theoretical study through mathematical abstraction will be done.

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